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Evolution of Epilepsy and EEG Findings in Angelman Syndrome

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Summary: *Purpose:* To evaluate the evolution of epileptic seizures and EEG features in a large group of patients with Angelman syndrome (AS).

Methods: Thirty-six patients with AS with a proven chromosome 15q11-13 deletion were retrospectively analyzed with regard to their epilepsy and EEG findings by examination of patient files and EEGs. All EEGs were reviewed by one of the authors. A logistic regression model, with a follow-up from 1 to 39 years (mean, 15 years), was used for statistical analysis.

Results: Epileptic seizures had occurred in 30 (83%) patients. In 43% of them, the initial symptoms of epilepsy were febrile convulsions in infancy. In childhood, epilepsy could start with almost any type of seizure. Atypical absences and myoclonic seizures prevailed in adulthood. Epileptic seizures were present in 92% of the adult patients. The most typical EEG findings were rhythmic triphasic delta waves of high amplitude with a maximum over the frontal regions, identified in 99 (66%) of 150 EEGs, and continuously or intermittently, in 30 (83%) of 36 patients with AS. In 47% it was present even before a clinical diagnosis of AS was considered. High-amplitude rhythmic 4–6/s slow activity, seen in 44 (29%) of 150 EEGs, was not present after the age of 12 years.

Conclusions: In contrast to previous reports suggesting a decreasing frequency of epileptic seizures with age, we found that 92% of the adult patients with AS continued to have epileptic seizures. The most typical EEG finding in AS, in both children and adults, was the presence of frontal triphasic delta waves. In mentally retarded patients, this EEG pattern should point the physician in the direction of AS. **Key Words:** Angelman—Epilepsy—EEG—Follow-up.

In 1965, Angelman described three unrelated mentally retarded children with a typical facial appearance: microcephaly with occipital flattening, frequent tongue protrusions, apparent prognathism, particular ocular features such as blue eyes, chorioidal pigment hypoplasia, strabismus, and easily provoked, prolonged paroxysms of laughter, epileptic seizures, and EEG abnormalities (1). The ataxic jerky movements of the extremities were reminiscent of those of a puppet on a string, prompting the term "puppet children." About 400 cases of AS have since been reported (1–17), including familial cases. High-resolution chromosome banding analysis has detected chromosome 15q11-13 deletions in ~60% of patients with AS. By using specific DNA probes, a molecular deletion can be found in ~80% of patients with AS (18–20). The deleted chromosome 15 is of maternal origin (21). A small percentage of patients with AS show paternal uniparental disomy or a localized methylation defect (20). Although epilepsy occurs in ~80–90% of the patients with AS (12,15–17), few studies have reported the follow-up of epileptic seizures (1,2,6–8,15,22) and EEG findings (2,4,9,11,15,22–24). There is a perception that patients with AS have epileptic seizures only in childhood and that the typical EEG patterns of childhood do not occur in adults (12,23). The purpose of our study was to examine these aspects in young and adult patients with AS. We performed a retrospective study of the long-term evolution of epileptic seizures and EEG findings in 36 patients with AS with a 15q11-13 deletion.

PATIENTS AND METHODS

The sample consisted of 36 patients with AS with a maternal 15q11-13 deletion determined by restriction

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fragment length polymorphism (RFLP) analysis or cytogenetic analysis by using chromosome 15 markers. None of the patients had paternal uniparental disomy. Patient files were collected from three University Hospitals, one general hospital, and five institutions for the mentally disabled. The types of seizures and types of epilepsy were classified according to the Classification of The International League Against Epilepsy (25,26). All patients had undergone one or more EEG examinations, by using the international 10-20 system, without sedation. All EEGs were personally reanalyzed by the first author, paying special attention to the presence of three abnormal patterns described as being characteristic for AS (23): (a) persistent rhythmic 4–6/s activity with amplitudes >200 μV not associated with drowsiness; (b) prolonged runs of rhythmic 2–3/s activity (200–500 μV), most prominent in the frontal regions, sometimes associated with discharges (ill-defined spike/wave complexes); and (c) spikes mixed with 3–4/s components, usually >200 μV, mainly posterior and facilitated by, or only seen with, eye closure. Eye closure was not always obtained in these hyperactive and severely retarded children. In addition, the EEGs were scored for the presence of one of the following patterns: N, abnormal EEG without spikes (for instance, background rhythm too slow for age); H, high-voltage EEG with or without spikes; F, focal spikes or multifocal spikes; S, diffuse spike and waves; and C, continuous (>20 s) diffuse spike-and-wave bursts.

Statistical analysis

Our study assessed how the probabilities of epileptic seizures and EEG characteristics evolve with increasing age. Such dependencies may be studied by comparing different subjects at different ages (cross-sectionally) or by studying the same subjects (longitudinally). Our sample of 36 patients was observed a varying number of times at varying ages; the study is, therefore, a mixture of a cross-sectional and a longitudinal study. The logistic regression model with random patient effects is able to estimate the dependence of epilepsy and EEG characteristics on age in a mixed sample. Basically, different patients at different ages are compared simultaneously with a comparison of the same patients at different ages (27). The results are illustrated graphically with the marginal probability of epilepsy or the occurrence of EEG parameters as a function of age.

RESULTS

Evolution of epileptic seizures

Thirty-six patients with AS (20 male and 16 female patients) were studied. Mean age was 11 years (range, 1.5–39 years); age at diagnosis ranged from 1 to 32 years (mean, 10.2 years). Epileptic seizures occurred in 30 (83%) patients. Age at onset varied from 1 month to 5 years (mean, 2 years). The follow-up period ranged from 1 to 39 years (mean, 15 years). In our group, the percentage having epileptic seizures increased rapidly after the age of 5 years to ~90% in adulthood (Fig. 1). Initial seizure types were tonic–clonic (12), atypical absences (10), myoclonic (three), tonic (three), or generalized convulsive status epilepticus (two patients). Thirteen (43%) of 30 patients had febrile seizures. Only two did not develop epilepsy. Their follow-up is too short to allow any conclusions at this time. Tonic–clonic status epilepticus occurred during follow-up in five patients. Three of them had status epilepticus more than once. During follow-up, three patients had an absence status and five a myoclonic status epilepticus. The myoclonic status often occurred more than once in childhood as in adulthood. In adults (older than 18 years; 14 patients), the main seizure types were atypical absence seizures (five), myoclonic seizures (five), or a combination of the two (three patients). Epileptic seizures were present in 13 (92%) of 14 adult patients with AS. One patient is still seizure free at age 21 years and has never had an epileptic seizure. Antiepileptic drugs (AEDs) resulted in complete seizure control in five patients. These patients had the following seizure types: atypical absences (two patients treated with valproate (VPA) and phenobarbital (PB), and carbamazepine (CBZ) and clonazepam (CZP), respectively); a combination of atypical absences and myoclonic seizures (one patient; treatment with CZP); and tonic–clonic seizures (two patients; treatment with VPA and PB, respectively). Decreasing the dosage of AEDs in these patients led to recurrence of seizures. Eight patients were still having epileptic seizures despite AEDs; three had atypical absences [treatment with VPA (two patients) or PB (one patient)]; one had myoclonic seizures

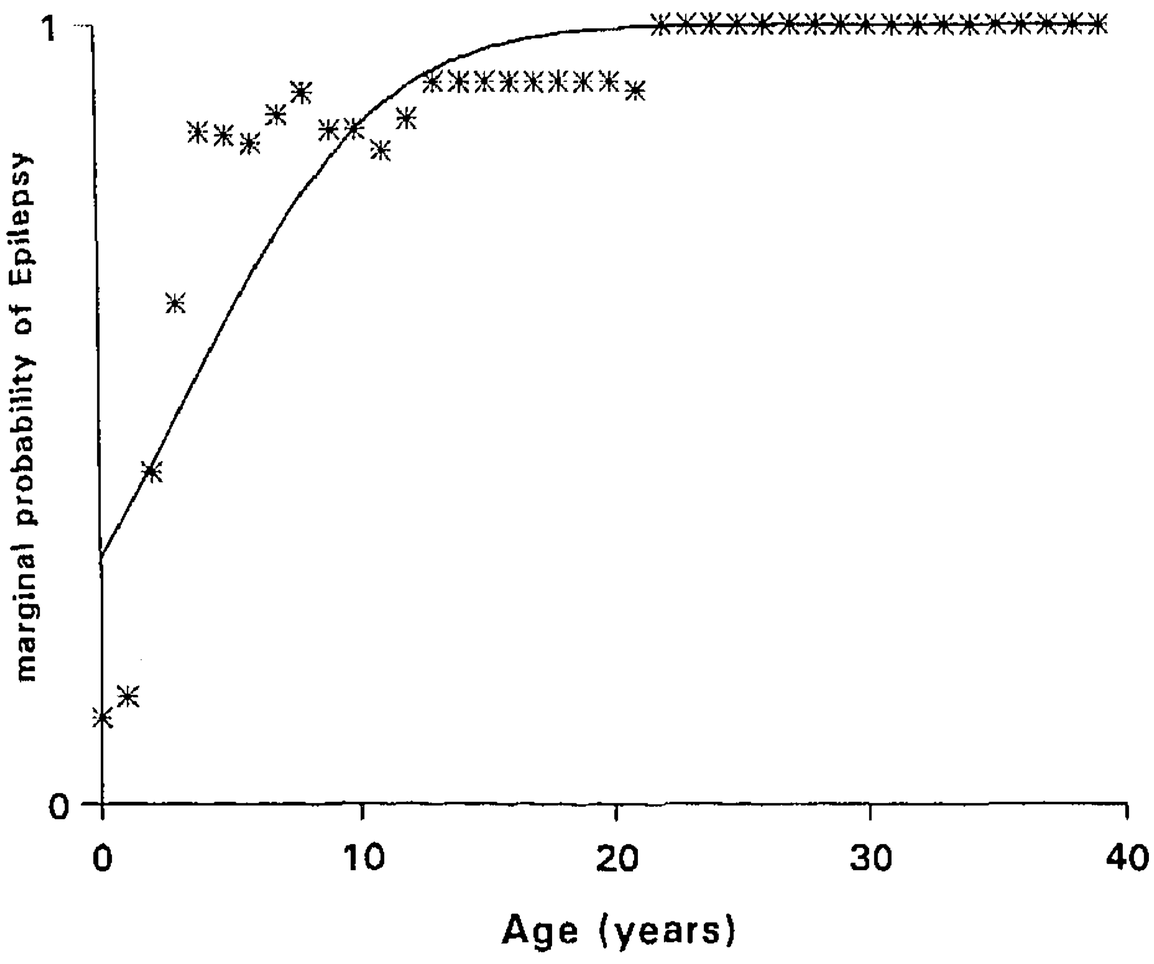

FIG. 1. Estimated marginal probability of having epileptic seizures is shown as a function of age according to the logistic regression model. Asterisks denote the observed proportions of patients with epilepsy.

(with a combination of PB and phenytoin); one had both absences and myoclonic seizures (treatment with VPA and CZP). The other three patients had a combination of myoclonic seizures (three patients), tonic–clonic seizures (two patients), complex partial seizures (two patients), and atypical absences (one patient); their AEDs varied from two to five drugs. Seizures were often difficult to control, especially in early childhood; in adulthood, they could play an important role in daily life. The most effective treatment was VPA (eight patients), a combination of VPA and CZP (six patients), or other benzodiazepines (two patients), or PB (three patients). Four of seven patients who had been treated with CBZ showed an increase of epileptic seizures during treatment (one patient had an increase of myoclonic seizures, one patient, of atypical absences, one developed more tonic–clonic seizures, and one had more complex partial seizures).

Evolution of EEGs

All 36 patients with AS had undergone at least one EEG examination (total, 150 EEGs). Thirty patients had had two or more EEGs (mean, 4.2 ± 3.6 EEGs). Six patients had had one EEG; eight patients, two; eight, three EEGs; and 14 patients, more than three. The age at which the first EEG was made varied between 1 month

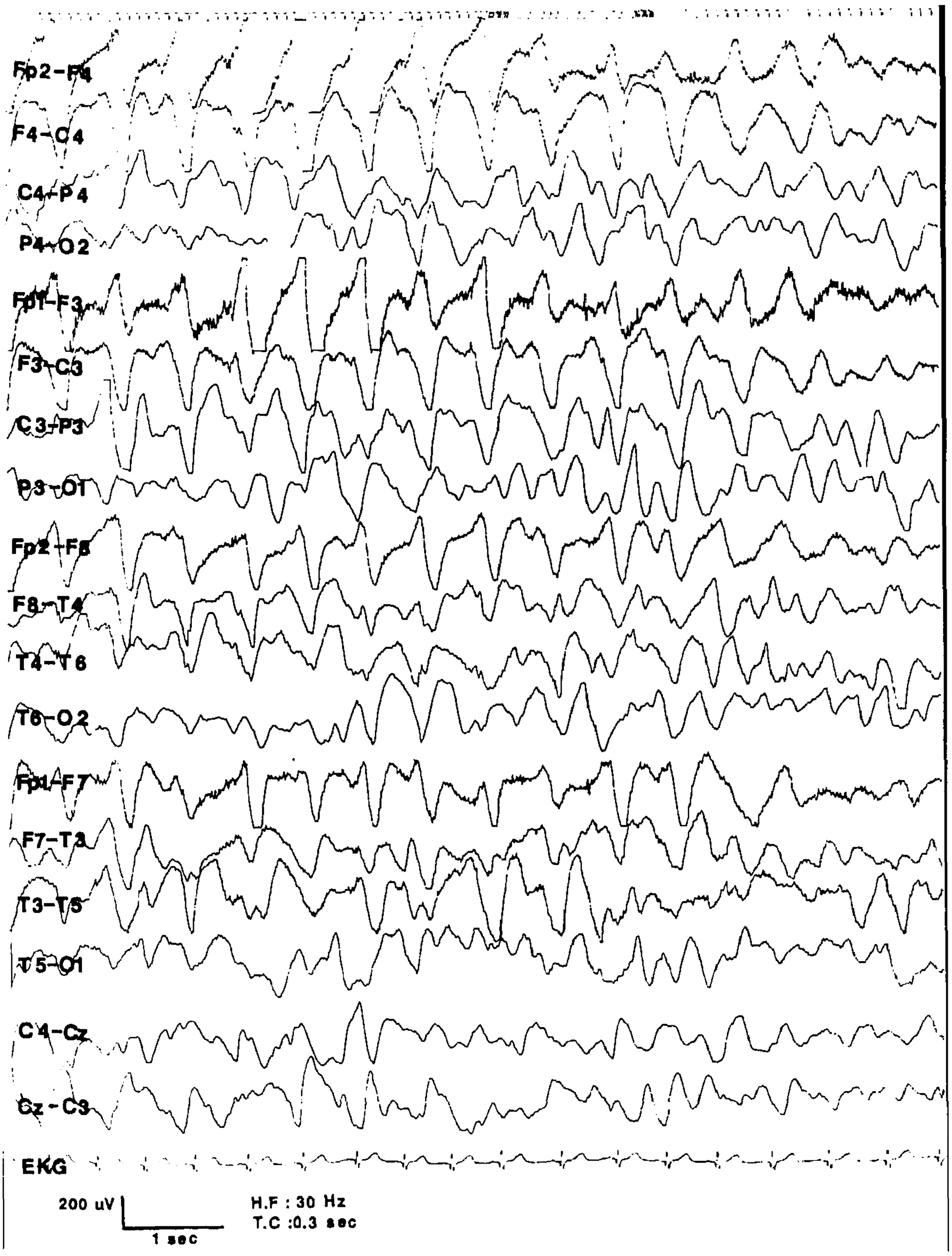

FIG. 2. Typical triphasic delta waves with a maximum over the frontal regions in a 3-year-old patient with Angelman's syndrome with atypical absence seizures.

and 18 years (mean, 3.5 yrs), whereas the age at which the last EEG was made ranged from 2 months to 33 years (mean, 9.6 years). In 30 patients, the first EEG was recorded 2 months to 23 years (mean, 7.5 yrs) before the diagnosis of AS was established.

The most frequently occurring pattern [30 (83%) of 36 patients with AS] consisted of rhythmic triphasic 2- to 3-Hz high-voltage (200–500 μV) activity, mixed with spikes or sharp waves with a maximum over the frontal regions (Fig. 2). This pattern was seen in 99 EEGs; it was continuous in 72 and intermittent in 27. In 16 of the 30 patients, this pattern was found in successive EEGs. EEGs were recorded in eight of 14 adults; five of them also showed this specific pattern. Of the 30 patients with this typical EEG pattern, only two had never had an epileptic seizure, but a short follow-up in some patients precluded a definite conclusion. Of the six patients without triphasic wave activity, four have so far not had an epileptic seizure; their follow-up ranged from 3 to 12 years (mean, 6 years). The other two have been seizure free with AEDs for >5 years. This EEG pattern was present in 17 (47%) of 36 patients before a clinical diagnosis of AS was made. The probability of having triphasic waves increased with age (Fig. 3).

High-voltage rhythmic 4- to 6-Hz slow activity (>150–500 μV), with or without spikes, was seen in 22 patients (44 EEGs). After age 12 years, this pattern (H) disappeared (Fig. 4) and changed to intermittent and sometimes continuous triphasic delta activity with a maximum over the frontal regions or to focal (F) or multifocal spikes (S) with a background rhythm too slow for age (N). The EEG recordings of the six patients without epileptic seizures showed abnormalities in all but one; this child had undergone an EEG at age 10 weeks because of feeding problems. The other patients showed high-voltage 3-Hz activity and 4- to 6-Hz rhythmic activity in the frontal regions without spikes, or a background rhythm too slow for age.

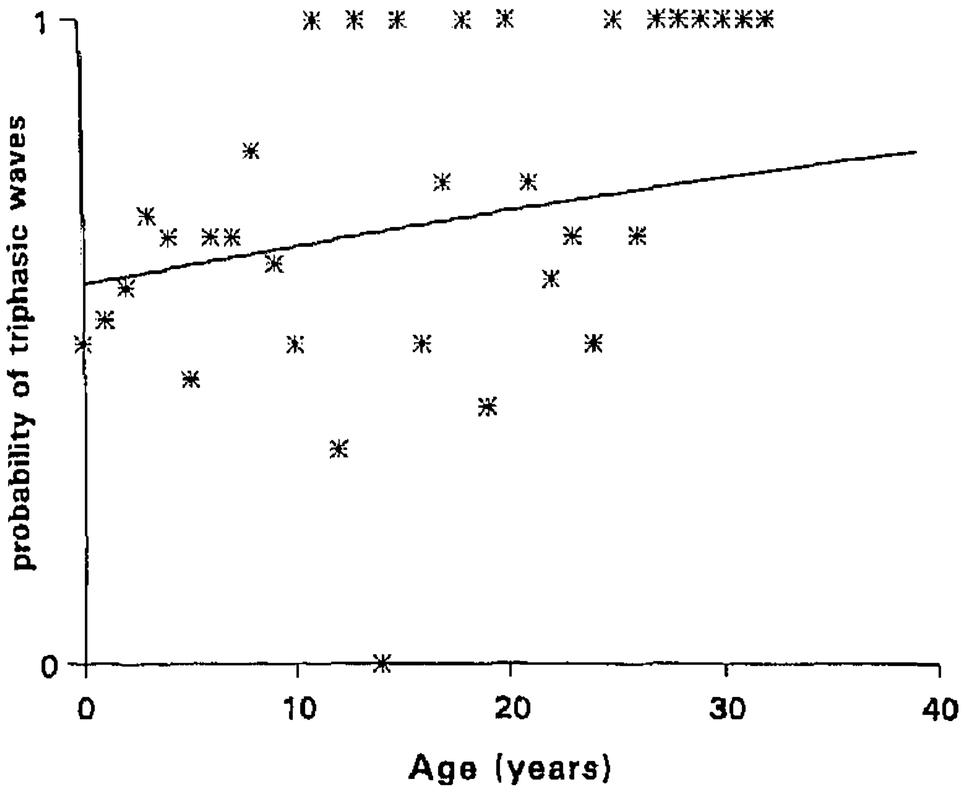

FIG. 3. Estimated marginal probability of triphasic delta waves, with a maximum over the frontal regions, being present in EEG recordings as a function of age according to the logistic regression model. Asterisks denote the observed proportions of EEGs with this pattern.

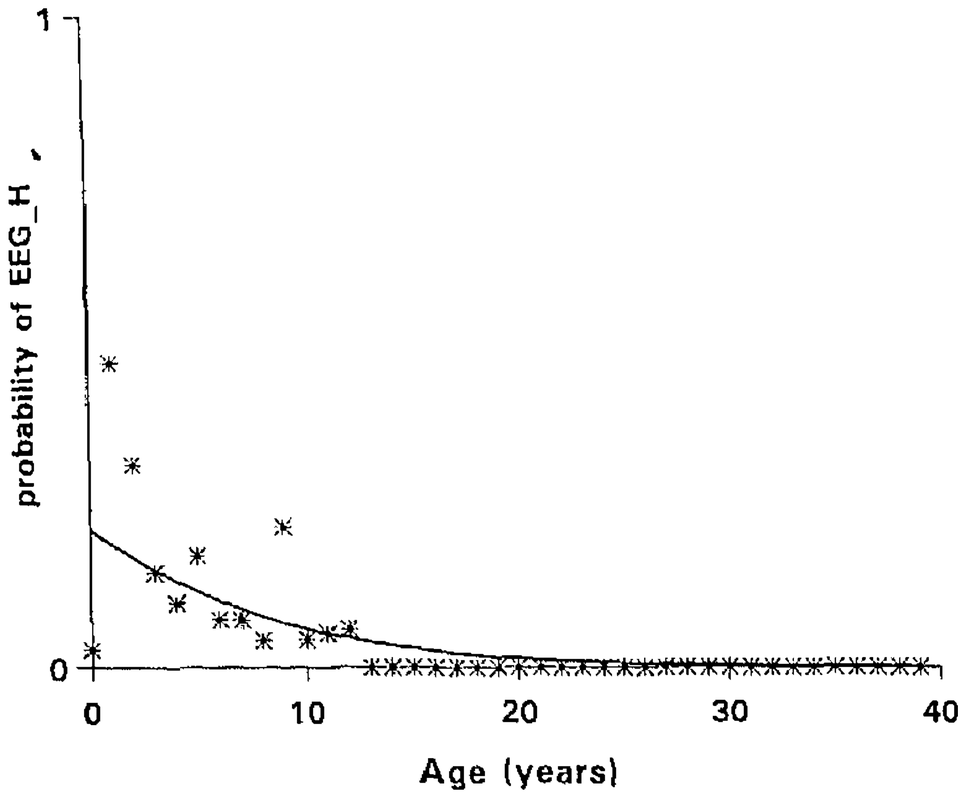

FIG. 4. Probability of high-amplitude rhythmic 4–6/s slow activity, with or without spikes (H), being present in EEG recordings as a function of age according to the logistic regression model. Asterisks denote the observed proportions of EEGs with this pattern.

Eight of the 36 patients were asked to close their eyes during one or more EEG recordings; five of them showed spikes/sharp waves mixed with large-amplitude 3- to 4-Hz components in the posterior areas on eye closure.

DISCUSSION

We found characteristic features of epilepsy in 36 patients with AS with a chromosome 15q11-13 deletion. Seizures started in infancy or early childhood (30 of 36), in some patients during a febrile period (13 of 36). In the study of Viani et al. (17), 11 of 18 patients with AS showed febrile seizures. In childhood, a diversity of seizures was observed: tonic–clonic seizures, atypical absence seizures, myoclonic seizures, tonic seizures, and status epilepticus. Absence status and myoclonic status epilepticus also were found. In our study, a status myoclonicus was found in 16% of patients with AS, occurring in childhood as well as in adults. Viani et al. (17) reported a myoclonic status epilepticus in nine of 18 patients with AS during long-lasting periods of jerky movements. We cannot confirm these findings, because our EEG studies were not performed during the previously mentioned periods. In adulthood, atypical absence seizures, myoclonic seizures, or a combination of the two were most prominent. Matsumoto et al. (22) reported atypical absence seizures in eight and an atypical absence status in four of eight patients with AS. They also described almost every seizure type in infancy and later myoclonic seizures, atypical absence seizures, and astatic seizures. We did not find astatic seizures in our patients. A significant decrease of incidence of epileptic seizures has been reported with increasing age (12,17, 22); in our study, however, 92% of the adult patients with AS still experienced epileptic seizures. This dis-

crepancy can be explained by the fact that most authors examined only children with AS. The most effective AEDs were VPA in combination with CZP or other benzodiazepines, whereas CBZ sometimes had an adverse effect. This also was described by others (17). In adult patients with AS, PB was also effective. In accordance with other authors (2,4,22,23), we found that there are specific EEG patterns in patients with AS, which may appear in isolation or in various combinations, either in the same EEG recordings or at different times in the same patient. The most frequently occurring EEG pattern in our patients with AS was rhythmic triphasic 2- to 3-Hz, high-voltage (200–500 μV) activity, mixed with spikes or sharp waves with a maximum over the frontal regions. It had occurred before a clinical diagnosis was considered in 47% of these children, probably because of early screening for retardation or an EEG examination after a first epileptic seizure. This specific EEG pattern usually persisted in adulthood. The eye-closure test was seldom possible in these hyperactive and severely retarded children. We cannot, therefore, confirm the findings of Boyd et al. (23) that eye closure in patients with AS facilitates spikes mixed with 3- to 4-Hz high-voltage components (>200 μV). Similar patterns of high-amplitude rhythmic triphasic 2- to 3-Hz activity in patients with AS can be seen in EEGs reported by other authors (2,11,17,22,23). It has previously been labeled hypsarrhythmia (West syndrome, WS) or the petit mal variant pattern (Lennox–Gastaut syndrome, LGS) (15). In our view, the EEG in AS differs from that in WS or LGS. As has been described by Boyd et al. (23), the high-voltage persistent 5- to 6-Hz rhythms are seen only in children—in our study, younger than 12 years. Although a clinical diagnosis of AS remains difficult at an early age and sometimes in adults, EEGs can play an important role. The previously mentioned EEG pattern in a mentally retarded patient should suggest a diagnosis of AS. Further investigations, especially EEGs of patients with AS without a detectable deletion, are currently under way.

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REFERENCES

1. Angelman H. "Puppet" children: a report on three cases. *Dev Med Child Neurol* 1965;7:681–8.
2. Bower BD, Jeavons PM. The "happy puppet" syndrome. *Arch Dis Child* 1967;42:298–302.
3. Berg JM, Pakula Z. Angelman's ("happy puppet") syndrome. *Am J Dis Child* 1972;123:72–4.
4. Mayo O, Nelson MM, Townsend HRA. Three more "happy puppets." *Dev Med Child Neurol* 1973;15:63–74.
5. Dooley JM, Berg JM, Pakula Z, MacGregor DL. The puppet-like syndrome of Angelman. *Am J Dis Child* 1981;135:621–4.
6. Hersh JH, Bloom AS, Zimmerman W, et al. Behavioral correlates in the happy puppet syndrome: a characteristic profile? *Dev Med Child Neurol* 1981;23:792–800.
7. Bjerre I, Fagher B, Ryding E, Rosen I. The Angelman or "happy puppet" syndrome: clinical and electroencephalographic features and cerebral blood flow. *Acta Paediatr Scand* 1984;73:398–402.
8. Dorries A, Spohr HL, Kunze J. Angelman ("happy puppet") syndrome: seven new cases documented by cerebral computed tomography: review of the literature. *Eur J Pediatr* 1988;148:270–3.
9. Ganji S, Duncan MC. Angelman's (happy puppet) syndrome: clinical, CT scan and serial electroencephalographic study. *Clin Electroencephalogr* 1989;20:128–40.
10. Zori RT, Hendrickson J, Woolven S, et al. Angelman syndrome: clinical profile. *J Child Neurol* 992;7:270–80.
11. Pampiglione G, Martinez A. Evolution of Angelman syndrome: follow-up of three new cases. *Electroencephalogr Clin Neurophysiol* 1983;56:72P.
12. Clayton-Smith J. Clinical research on Angelman syndrome in the United Kingdom: observations on 82 affected individuals. *Am J Med Genet* 1993;46:12–5.
13. Buntinx IM, Hennekam CM, Brouwer OF, et al. Clinical profile of Angelman syndrome at different ages. *Am J Med Genet* 1995;56:176–83.
14. Williams CA, Angelman H, Clayton-Smith J, et al. Angelman syndrome: consensus for diagnostic criteria. *Am J Med Genet* 1995;56:237–8.
15. Sugimoto T, Yasuhara A, Ohta T, et al. Angelman syndrome in three siblings: characteristic epileptic seizures and EEG abnormalities. *Epilepsia* 1992;33(6):1078–82.
16. Robb SA, Pohl KRE, Baraitser M, Wilson J, Brett EM. The "happy puppet" syndrome of Angelman: a review of the clinical features. *Arch Dis Child* 1989;64:83–6.
17. Viani F, Romeo A, Viri M, et al. Seizure and EEG patterns in Angelman's syndrome. *J Child Neurol* 1995;10:467–71.
18. Williams CA, Gray BA, Hendrickson JE, Stone JW, Cantu ES. Incidence of 15q deletion in the Angelman syndrome: a survey of twelve affected persons. *Am J Med Genet* 1989;32:339–45.
19. Pembrey M, Fennel SJ, van den Berghe J, et al. The association of Angelman's syndrome with deletions within 15q11-13. *J Med Genet* 1989;26:73–7.
20. Knoll JHM, Glatt KA, Nicholls RD, et al. Chromosome 15 uniparental disomy is not frequent in Angelman syndrome. *Am J Hum Genet* 1991;48:16–21.
21. Knoll JHM, Nicholls RD, Magenis RE, et al. Angelman and Prader-Willi syndrome share a common chromosome 15 deletion but differ in parental origin of the deletion. *Am J Med Genet* 1989;32:285–90.
22. Matsumoto A, Kumagai T, Miura K, Miyazaki S, Hayakawa C, Yamanaka T. Epilepsy in Angelman syndrome associated with chromosome 15q deletion. *Epilepsia* 1992;33:1083–90.
23. Boyd SG, Harden A, Patton MA. The EEG in early diagnosis of the Angelman (happy puppet) syndrome. *Eur J Pediatr* 1988;147:508–13.
24. Jeavons PM, Moore JR. The EEG in happy puppet syndrome. *Electroencephalogr Clin Neurophysiol* 1972;33:346–8.
25. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;22:489–501.
26. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389–99.
27. Fitzmaurice GM, Laird NM. A likelihood-based method for analysing longitudinal binary responses. *Biometrika* 1980;67:141–51.